American Journal of Epidemiology
Vol. 168, No. 8
DOI: 10.1093/aje/kwn194
Advance Access publication August 13, 2008

Original Contribution

Cigarette Smoking and the Development of Premenstrual Syndrome

Elizabeth R. Bertone-Johnson, Susan E. Hankinson, Susan R. Johnson, and JoAnn E. Manson

Received for publication April 17, 2008; accepted for publication June 4, 2008.

Moderate to severe premenstrual syndrome (PMS) affects as many as 20% of premenopausal women. Although smoking may be more common in women with PMS, it is unknown whether smoking is involved in PMS etiology. In 1991–2001, the authors conducted a case-control study nested within the prospective Nurses' Health Study II. Participants were US women aged 27–44 years and free of PMS at baseline, including 1,057 who developed PMS over 10 years and 1,968 reporting no diagnosis of PMS and only minimal menstrual symptoms during this time. Smoking at various ages was assessed by questionnaires. After adjustment for oral contraceptives and other factors, current smokers were 2.1 times as likely as never smokers to develop PMS over the next 2–4 years (95% confidence interval: 1.56, 2.83). Total pack-years and smoking during adolescence and young adulthood were also independently associated with a higher risk of PMS. For example, the relative risk for women who started smoking before age 15 years, compared with never smokers, was 2.53 (95% confidence interval: 1.70, 3.76). Results suggest that smoking, especially in adolescence and young adulthood, may increase risk of moderate to severe PMS. These findings may provide an additional incentive for young women to avoid cigarette smoking.

case-control studies; cohort studies; menstrual cycle; premenstrual syndrome; smoking

Abbreviation: PMS, premenstrual syndrome.

Premenstrual syndrome (PMS) is one of the most common disorders in women, yet little is known about factors that influence its development. PMS is characterized by the occurrence of physical and emotional symptoms such as breast tenderness, bloating, depression, and irritability in the luteal phase of the menstrual cycle (1, 2). Although most women's symptoms are mild, 15%–20% of women experience PMS symptoms severe enough to interfere with normal activities and interpersonal relationships (3–5). Because of the drawbacks associated with many pharmaceutical treatments (5, 6), it is essential to identify ways for women to easily modify their risk of developing moderate to severe PMS.

Cigarette smoking may plausibly influence the development of PMS through its effect on estrogen, progesterone, androgen, and gonadotropin levels (7–9), which may be involved in the etiology of PMS (10, 11). Few previous studies have compared the frequency of smoking among women who currently have PMS with the frequency among controls without the disorder (3, 4, 12–14). Results have been inconsistent, but they generally suggest that smoking may be more common in prevalent PMS cases. However, it is unknown whether smoking is involved in the underlying etiology of PMS or whether women experiencing PMS smoke as a means of treating their symptoms.

To address these questions, we assessed the relation between smoking and the initial development of moderate to severe PMS in a case-control study nested within a large prospective study.

MATERIALS AND METHODS

The Nurses' Health Study II is a cohort of 116,678 US female registered nurses who responded to a mailed questionnaire in 1989. The participants were aged 25–42 years at the time of the initial mailing and provided information on their medical history and health-related behaviors, such as use of oral contraceptives, menstrual and pregnancy history,

Correspondence to Dr. Elizabeth R. Bertone-Johnson, Arnold House, University of Massachusetts, 715 North Pleasant Street, Amherst, MA 01003-9304 (e-mail: ebertone@schoolph.umass.edu).

and smoking status. Cohort members have completed questionnaires every 2 years thereafter to update information on behaviors and identify new disease diagnoses. The protocol for this study was approved by the institutional review board at the Harvard School of Public Health.

The Nurses' Health Study II PMS substudy

Our procedure for identifying PMS cases and controls has been discussed in detail previously (15, 16). Briefly, information on PMS was first collected on the baseline Nurses' Health Study II questionnaire (1989), when participants were asked whether they had ever received a physician diagnosis of the disorder. On subsequent questionnaires in 1993, 1995, 1997, and 2001, participants were asked whether they had received a new diagnosis of PMS during the previous 2–4-year period and, if so, the time period when the diagnosis was made.

In January 2002, we conducted a substudy among participants to identify PMS cases and controls without PMS. We identified all members of the cohort who had not reported a diagnosis in 1989 or 1991 and were thus considered at risk of incident PMS at the start of follow-up. To make the timing of comparisons between cases and noncases as similar as possible, we assigned each woman a ''reference year.'' For cases who reported a new diagnosis of PMS on a study questionnaire (1993–2001), the reference year equaled the year of diagnosis. Because controls not reporting PMS did not have a year of diagnosis, we assigned each a randomly chosen reference year (1993–2001). We then used these reference years to determine eligibility for the PMS substudy, measure menstrual symptom experience, and assess smoking status.

To reduce the likelihood of including women with menstrual-type symptoms attributed to causes other than PMS, we excluded women who had reported a diagnosis of cancer, endometriosis, usually irregular menstrual cycles, or infertility before their reference year. Furthermore, to assure that both cases and noncases were premenopausal, we restricted inclusion to women who had not reported menopause or a hysterectomy before their reference year. From among all remaining eligible women, we selected 6,000 women for the PMS substudy, including 3,430 who reported a new diagnosis of PMS and 2,570 who did not report PMS. For case selection, we gave preference to women with recent reference years; noncases were then frequency matched to cases by reference year.

We mailed participants a 2-page questionnaire based on the Calendar of Premenstrual Experiences designed by Mortola et al. (1). Women were asked to report whether in the specific 2-year period before their reference year they had experienced 26 different symptoms ''most months of the year for at least several days each month before [their] menstrual period begins.'' We also asked about the age at which symptoms first occurred, the timing of symptom onset and cessation during an average menstrual cycle, symptom severity, and whether symptoms interfered with life activities and interpersonal relationships. Completed questionnaires were received from 2,966 women (86.5%) self-reporting and 2,504 women (97.4%) not reporting PMS.

Because the severity of premenstrual symptoms varies considerably between women, it was important to identify from among all women self-reporting PMS those who experienced moderate to severe symptoms that substantially impaired their quality of life. We thus used information provided on the supplemental questionnaire to identify women self-reporting PMS who also met our case definition, based on criteria established by Mortola et al. (1). We defined cases as women with 1) at least 1 physical and 1 affective menstrual symptom; 2) overall menstrual symptom severity classified as moderate or severe, or effect of symptoms on life activities and social relationships classified as moderate or severe; 3) symptoms beginning within 14 days of the onset of menses; 4) symptoms ending within 4 days after the onset of menses; and 5) symptoms absent in the week after menses ends. Overall, 1,057 (35.6%) of the women who initially self-reported PMS also met these criteria and were included as ''validated'' PMS cases in the subsequent analysis. We then identified from among participants who had not reported a PMS diagnosis those women who experienced either no menstrual symptoms or only mild symptoms that had no substantial effect on life activities and relationships. A total of 1,968 of the 2,504 noncases (78.6%) met these criteria and were included in subsequent analyses as ''validated'' controls.

The validity of our approach to identifying PMS cases and controls was assessed previously (16). Briefly, participants included 135 members of the Nurses' Health Study II PMS substudy who first reported PMS by questionnaire in 2001 and 371 who never reported PMS (1989–2001). We found that menstrual symptom occurrence, timing, and severity in women meeting criteria based on those established by Mortola et al. (1) as assessed by our retrospective questionnaire were essentially identical to those for women who also reported clinician-supervised prospective symptom charting as part of their diagnosis.

Assessment of cigarette smoking and other factors

Information on smoking behavior was first measured on the baseline Nurses' Health Study II questionnaire in 1989. Women were asked whether they had smoked 20 or more packs of cigarettes in their lifetime and, if so, if they currently smoked cigarettes or had quit less than 1 or 1 or more years ago. Current and former smokers were asked about the average number of cigarettes smoked (1–4, 5–14, 15–24, 25–34, 35–44, $\geq$45 cigarettes/day). In addition to current smoking, we also inquired about the age at which women started smoking and the number of cigarettes smoked per day at specific ages (before age 15, 15–19, 20–24, 25–29 years). On each subsequent biennial questionnaire (1991–2001), women were asked whether they currently smoked and the number of cigarettes smoked per day. Total duration of smoking was calculated based on smoking status at each age queried and on each Nurses' Health Study II questionnaire. For each time period, we calculated pack-years of smoking by multiplying the total duration of smoking in years by the number of packs of cigarettes smoked per day.

We collected information on other factors potentially associated with PMS and smoking throughout the study

period. Information on age, body weight, number of full-term pregnancies (i.e., pregnancies of ≥6 months), age at first birth, tubal ligation, and oral contraceptive use was updated biennially. Age at menarche, menstrual cycle characteristics, weight at age 18 years, and height were assessed in 1989. Physical activity level was measured in 1991 and 1997 and was used to calculate metabolic-equivalent hours per week (17). Early life stress related to punitive parenting during childhood and adolescence was assessed in 2001 by supplemental questionnaire and was used to calculate a childhood trauma score, ranging from 5 (no report of trauma) to 25 (report of severe trauma) (18). Macro- and micronutrient intake was measured by semiquantitative food frequency questionnaire in 1991, 1995, and 1999, and nutrients were adjusted for total energy intake by the residual method (19). Finally, our supplemental menstrual symptom questionnaire inquired whether women had been diagnosed with depression or had taken antidepressants, and the timing of each.

Statistical analysis

We divided participants into never smokers, former smokers, and current smokers based on their smoking status at 1) baseline (1991), 2) during the 2-year period immediately preceding their individual reference year, and 3) during specific ages. For each time period, current and former smokers were subdivided on the basis of the number of cigarettes smoked per day. The total duration of smoking and pack-years were classified into 5-year categories. We then categorized women on the basis of the age at which they started smoking (<20, 20–24, ≥25 years), whether or not they started smoking before the age at which menstrual symptoms started, and, for former smokers, the age at which they quit smoking.

We compared baseline characteristics of PMS cases and controls with *t* tests and Pearson's chi-squared tests. We used odds ratios to estimate the relative risk of PMS for women across categories of smoking and calculated 95% confidence intervals. All statistical analyses were conducted with SAS software (SAS Institute, Inc., Cary, North Carolina). Multivariable analyses were adjusted for age; diagnosis year; number of full-term pregnancies; body mass index (weight (kg)/height $(m)^2$); tubal ligation; duration of oral contraceptive use; antidepressant use; and intake of calcium, vitamin D, alcohol, vitamin B_6, and potassium from foods and supplements. Several additional variables were not included in the final analysis because they were unrelated to the development of PMS and/or smoking, including age at first birth; physical activity; body mass index at age 18 years; and dietary intake of magnesium, manganese, vitamin E, linolenic acid, total carotenoids, and caffeine. The Mantel-extension test for trend was used to evaluate linear trend across categories by modeling the median value of each category as a continuous variable in the multivariable regression models; *P* values were 2 sided.

In a subanalysis limited to PMS cases ($n = 1{,}057$), we assessed whether the occurrence of specific symptoms was associated with smoking. We calculated multivariable relative risks for each symptom, comparing women who reported current smoking in their year of diagnosis with never smokers. In addition, we calculated similar risk estimates based on smoking status at ages 15–17 years.

We assessed whether the relation between smoking and risk of PMS was modified by body mass index (<25.0 vs. ≥25.0 kg/m^2). Interactions were considered statistically significant if the Wald 2-sided *P* value for the interaction term in the multivariable model was <0.05. Finally, we repeated our analyses in subgroups limited to women with no history of depression prior to their reference year and by excluding women using oral contraceptives at the start of follow-up (1991).

Table 1. Age-standardized Characteristics of Premenstrual Syndrome Cases and Controls at Baseline (1991),[a] Nurses' Health Study II Premenstrual Syndrome Substudy

Characteristic[b]	Cases ($n = 1{,}057$)	Controls ($n = 1{,}968$)	*P* Value[c]
Age, years	34.4 (4.3)	35.0 (3.9)	<0.001
Body mass index in 1991, kg/m^2	24.6 (0.2)	23.7 (0.1)	<0.0001
Body mass index at age 18 years, kg/m^2	21.4 (0.1)	21.1 (0.07)	0.03
Age at menarche, years	12.4 (0.04)	12.5 (0.03)	0.08
No. of full-term pregnancies	1.7 (0.04)	1.7 (0.03)	0.52
Age at first birth, years[d]	25.9 (0.1)	26.1 (0.1)	0.22
Physical activity, MET-hours/week[e]	22.9 (1.8)	23.3 (1.3)	0.88
Ever used oral contraceptives	85.7	77.7	<0.0001
History of tubal ligation	16.8	18.2	0.34
Ever used antidepressants	12.1	4.7	<0.0001

Abbreviation: MET, metabolic equivalent.

[a] All values are expressed as mean (standard error) or percentage. For age, the value in parentheses is the standard deviation versus standard error.

[b] All characteristics except age were standardized to the age distribution of cases and controls in 1991.

[c] Calculated by using the *t* statistic.

[d] Among parous women.

[e] Based on the method of Ainsworth et al. (17).

RESULTS

Compared with controls, PMS cases were slightly younger, had a higher mean body mass index at their reference year, and were more likely to have used antidepressants and oral contraceptives (Table 1; $P < 0.001$ for all). The 2 groups were similar regarding mean number of full-term pregnancies, age at first birth, history of tubal ligation, and physical activity level.

We observed a strong, positive relation between cigarette smoking and risk of incident PMS (Table 2). Compared with never smokers, current smokers had a multivariable-adjusted relative risk of 2.10 (95% confidence interval: 1.56, 2.83). Risk was also elevated for former smokers, with a relative risk of 1.80 (95% confidence interval = 1.07, 3.03) for

Table 2. Age- and Multivariable-adjusted Relative Risks of Premenstrual Syndrome by Smoking Status 2 Years Before the Reference Year in the Nurses' Health Study II Premenstrual Syndrome Substudy (1991–2001)

Smoking Level	No. of Cases	No. of Controls	Age-adjusted RR	Multivariable-adjusted RR[a]	95% CI
Smoking status[b]					
Never smoker	649	1,471	1.00	1.00	
Current smoker, no. of cigarettes/day	133	122	2.54	2.10	1.56, 2.83
1–14	74	70	2.44	2.04	1.40, 2.99
15–24	43	40	2.53	2.13	1.31, 3.47
≥25	16	12	3.13	2.34	0.99, 5.55
				P trend = 0.76[c]	
Former smoker, no. of cigarettes/day	273	369	1.72	1.66	1.35, 2.05
1–14	148	223	1.50	1.47	1.14, 1.89
15–24	89	106	2.00	2.06	1.48, 2.87
≥25	36	40	2.18	1.80	1.07, 3.03
				P trend = 0.06[c]	
Duration of smoking, years[b]					
1–5	45	74	1.38	1.28	0.84, 1.94
6–10	91	132	1.52	1.42	1.04, 1.94
11–15	103	107	2.17	2.28	1.65, 3.17
16–20	94	81	2.74	2.24	1.58, 3.17
>20	71	98	1.87	1.73	1.20, 2.48
				P trend = 0.10[c]	
Pack-years of smoking[b]					
1–5	117	184	1.41	1.39	1.05, 1.83
6–10	109	134	1.87	1.79	1.33, 2.42
11–15	75	75	2.38	1.99	1.36, 2.91
16–20	57	55	2.52	2.41	1.57, 3.69
>20	46	44	2.74	2.19	1.36, 3.53
				P trend = 0.03[c]	

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Multivariable relative risks were adjusted for age (<30, 30–34, 35–39, ≥40 years), reference year (1993, 1994–1995, 1996–1997, 1998–1999, 2000–2001), parity (0, 1–2, 3–4 or ≥5 pregnancies lasting ≥6 months), oral contraceptive use and duration (never, 1–23, 24–71, 72–119, ≥120 months), body mass index (<20.0, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, ≥30.0 kg/m^2), history of tubal ligation (no, yes), antidepressant use (never, ever), childhood trauma score (5, 6–10, 11–15, ≥16), and dietary intake of alcohol, vitamin B_6, potassium, calcium, and vitamin D (each in quintiles).

[b] The reference group for all comparisons is never smokers. Numbers may not sum to 1,057 cases and 1,968 controls because of missing data on smoking status.

[c] Tests for trend were calculated over levels of exposed participants (i.e., excludes never smokers).

women reporting having formerly smoked 25 or more cigarettes per day. High total pack-years and longer duration of smoking prior to the reference year were each also associated with increased risk of PMS, with evidence of a positive dose-response relation for increasing pack-years ($P = 0.03$). Results based on smoking status at baseline were very similar to those based on reference year and are not shown here.

Table 3 presents multivariable results according to the timing of smoking, both without (model 1) and with (model 2) additional adjustment for total pack-years of smoking. Before adjustment for total pack-years, we found that women who started smoking before age 15 years had a significant 2.5-fold higher risk than never smokers of developing PMS (relative risk = 2.53, 95% confidence interval:

Table 3. Multivariable-adjusted Relative Risks of Premenstrual Syndrome According to Timing of Smoking in the Nurses' Health Study II Premenstrual Syndrome Substudy (1991–2001)

Smoking Level	No. of Cases	No. of Controls	Model 1[a]		Model 2[b]	
			RR	95% CI	RR	95% CI
Age at which smoking started, years[c]						
Never	649	1,471	1.00		1.00	1.00
<15	76	61	2.53	1.70, 3.76	1.90	1.17, 3.09
15–19	229	297	1.68	1.35, 2.10	1.35	0.99, 1.84
20–24	93	119	1.68	1.22, 2.31	1.41	0.98, 2.03
≥25	7	12	1.51	0.52, 4.43	1.19	0.37, 3.79
Timing of starting to smoke[c]						
Started before symptoms developed[d]	348	337	2.22	1.81, 2.72	1.73	1.28, 2.32
Started after symptoms developed	40	48	1.71	1.06, 2.75	1.39	0.83, 2.34
Smoking status before age 15 years, no. of cigarettes/day[c]						
1–14	53	42	2.63	1.65, 4.19	2.00	1.18, 3.41
≥15	23	19	2.32	1.15, 4.70	1.64	0.76, 3.57
Smoking status at ages 15–19 years, no. of cigarettes/day [c]						
1–14	228	270	1.89	1.51, 2.37	1.40	1.03, 1.90
≥15	74	88	1.54	1.07, 2.22	0.94	0.57, 1.55
Smoking status at ages 20–24 years, no. of cigarettes/day [c]						
1–14	171	222	1.63	1.27, 2.08	1.41	1.05, 1.91
≥15	193	203	2.07	1.61, 2.65	1.49	0.93, 2.39
Smoking status at ages 25–29 years, no. of cigarettes/day [c]						
1–14	105	137	1.73	1.27, 2.34	1.45	1.00, 2.09
≥15	157	163	2.12	1.62, 2.78	1.39	0.77, 2.50
Years since quitting, no.[c]						
>15	70	131	1.44	1.03, 2.03	1.31	0.91, 1.87
11–15	71	106	1.37	0.97, 1.95	1.10	0.73, 1.67
6–10	80	67	2.78	1.90, 4.06	2.25	1.44, 3.50
≤5	52	68	1.42	0.94, 2.15	1.11	0.68, 1.81
Current smokers	133	122	2.10	1.56, 2.82	1.45	0.91, 2.30

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age; year of diagnosis/reference year; parity; oral contraceptive use and duration; body mass index; history of tubal ligation; antidepressant use; alcohol intake; childhood trauma score; and dietary intake of vitamin B_6, potassium, calcium, and vitamin D. Refer to footnote a in Table 2 for the variable categories.

[b] Adjusted for all factors in model 1 and for total pack-years of smoking (category median was modeled as a continuous variable).

[c] The reference category for all analyses is never smokers. For each age, results for women who were ever smokers but who reported smoking 0 cigarettes per day during the specified ages are not shown. Numbers may not sum to 1,057 cases and 1,968 controls because of missing data on smoking status.

[d] Includes controls who reported no menstrual symptoms.

1.70, 3.76). Additional adjustment for pack-years attenuated results, but risk was still significantly higher (relative risk = 1.90, 95% confidence interval: 1.17, 3.09). Risk was also higher for women who started smoking before the age at which their menstrual symptoms began compared with those who started smoking after their menstrual symptoms developed (relative risk for smoking before symptoms started vs. never smoking = 1.73, 95% confidence interval: 1.28, 2.32; relative risk for smoking after symptoms started = 1.39, 95% confidence interval: 0.83, 2.34). We did not observe

a clear linear relation between the timing of smoking cessation and PMS; risk was modestly elevated for all former smokers compared with never smokers, including those who had quit more than 15 years before their reference year.

For all analyses of smoking behavior, results excluding women who used oral contraceptives at baseline (119 cases and 189 controls) were nearly identical to those from the main analysis. For example, the relative risk for more than 20 pack-years versus none was 2.23 (95% confidence interval: 1.36, 3.65; P for trend < 0.0001). Results excluding women reporting a diagnosis of depression prior to their reference year (175 cases and 149 controls) were also very similar to those from the main analysis. For example, the relative risk for women reporting more than 20 pack-years versus none was 1.92 (95% confidence interval: 1.13, 3.27; P for trend < 0.0001). We did not find evidence of modification of the smoking–PMS relation by body mass index.

In a subanalysis limited to PMS cases ($n = 1{,}057$), we evaluated whether smoking was related to the occurrence of 26 specific PMS symptoms (Table 4). Cases who smoked during adolescence (ages 15–19 years) had a significant 39%–41% higher risk of experiencing backaches, acne, and anger and a 30%–33% lower risk of headaches and insomnia. Cases who were current smokers at the time of PMS diagnosis were significantly more likely than never smokers to report acne, breast tenderness, and abdominal bloating. Other symptoms evaluated showed no statistically significant relation to smoking status.

Table 4. Multivariable-adjusted Relative Risks of Specific Menstrual Symptoms by Smoking Status at Ages 15–19 Years and at Year of Diagnosis Among Premenstrual Syndrome Cases ($n = 1{,}057$) in the Nurses' Health Study II Premenstrual Syndrome Substudy (1991–2001)

Symptom	Multivariable-adjusted[a] Risk of Symptom for Smokers vs. Never Smokers			
	Smoking at Ages 15–19 Years		Smoking at Year of Diagnosis	
	RR	95% CI	RR	95% CI
Backache	1.41	1.04, 1.91**	1.45	0.92, 2.27
Acne	1.40	1.01, 1.92**	2.09	1.30, 3.35**
Anger	1.39	1.01, 1.90**	1.31	0.82, 2.09
Mood swings	1.37	0.98, 1.91*	1.38	0.83, 2.28
Food cravings	1.31	0.93, 1.83	1.33	0.80, 2.21
Hot flashes	1.29	0.74, 2.25	1.48	0.67, 3.27
Tendency to cry easily	1.28	0.95, 1.73	1.51	0.95, 2.39*
Depression	1.27	0.94, 1.72	1.27	0.82, 2.00
Nausea	1.18	0.60, 2.34	0.89	0.31, 2.56
Anxiety	1.17	0.85, 1.61	1.01	0.62, 1.64
Hypersensitivity	1.15	0.85, 1.57	1.29	0.82, 2.04
Appetite changes	1.15	0.85, 1.57	1.15	0.73, 1.82
Abdominal cramping	1.11	0.81, 1.53	0.95	0.59, 1.54
Confusion	1.08	0.64, 1.79	0.67	0.28, 1.63
Diarrhea/constipation	1.08	0.80, 1.47	1.46	0.93, 2.29*
Abdominal bloating	1.03	0.76, 1.41	1.65	1.00, 2.73**
Breast tenderness	1.01	0.72, 1.41	1.80	1.02, 3.17**
Swelling in extremities	1.00	0.69, 1.45	1.17	0.68, 2.00
Desire for aloneness	0.98	0.72, 1.33	1.04	0.66, 1.66
Fatigue	0.97	0.72, 1.31	1.27	0.81, 2.00
Forgetfulness	0.95	0.65, 1.38	0.87	0.49, 1.57
Irritability	0.96	0.63, 1.47	0.90	0.48, 1.67
Palpitations	0.89	0.49, 1.60	1.15	0.50, 2.66
Dizziness	0.77	0.33, 1.76	0.49	0.11, 2.20
Headache	0.70	0.52, 0.95**	0.71	0.45, 1.12
Insomnia	0.67	0.45, 0.99**	0.57	0.31, 1.05*

Abbreviations: CI, confidence interval; RR, relative risk.
* $P < 0.10$; ** $P < 0.05$.
[a] Relative risks were adjusted for age; year of diagnosis/reference year; parity; oral contraceptive use and duration; body mass index; history of tubal ligation; antidepressant use; alcohol intake; childhood trauma score; and dietary intake of vitamin B_6, potassium, calcium, and vitamin D. Refer to footnote a in Table 2 for the variable categories.

DISCUSSION

Our findings suggest that cigarette smoking, especially during adolescence and young adulthood, may increase a woman's likelihood of developing moderate to severe PMS. We found that the risk of incident PMS tended to increase with the quantity of cigarette smoking and was significantly higher for women who began smoking during adolescence. To our knowledge, ours is the first longitudinal study to assess how smoking may impact a woman's risk of developing PMS. Previous studies that assessed smoking levels among women who already have PMS have been limited in their ability to determine whether smoking is etiologically related to the disorder or whether smoking behavior is instead influenced by menstrual symptom experience.

Our findings concerning smoking are consistent with those from previous studies of prevalent PMS and menstrual symptoms. Deuster et al. (4) reported a nonsignificant higher prevalence of smoking among PMS cases versus noncases (9.7% vs. 6.1%) (4). The prevalence of PMS was also nonsignificantly higher among long-term smokers and heavier smokers. Smoking was associated with a higher risk of prevalent PMS and/or menstrual problems such as cramping and irregular periods in 4 additional cross-sectional studies (12, 14, 20, 21) but not in 3 others (3, 13, 22).

Smoking may be related to the initial development of PMS by affecting premenopausal sex steroid and gonadotropin levels (7–9). Windham et al. (7) measured urinary estrogen, progesterone, and follicle-stimulating hormone levels over 3–4 menstrual cycles in 403 premenopausal women (7). Heavier smoking was associated with higher follicle-stimulating hormone, estrogen, and progesterone metabolite levels during the follicular phase and with lower progesterone levels during the luteal phase. Follicle-stimulating hormone levels were also higher in smokers during the follicular-to-luteal-phase transition, which occurred approximately 1 day earlier than in nonsmokers. Smoking has

also been associated with increased levels of testosterone in premenopausal women (9) and may potentially affect androstenedione and dehydroepiandrosterone sulfate levels (23, 24). Tobacco use has been associated with shorter menstrual cycle length and irregular cycles (25, 26). Finally, smoking may lower plasma vitamin D levels (27). Two recent studies have suggested that low plasma 25-hydroxyvitamin D (28) and low dietary vitamin D intake (15) may potentially increase the incidence and/or severity of PMS. In our study population at baseline, mean daily energy-adjusted vitamin D intake was somewhat lower in women smoking 1–24 cigarettes (355 IU) and 25 or more cigarettes (317 IU) per day compared with never smokers (398 IU; $P = 0.0001$).

In addition to evaluating the relation between smoking and initial development of moderate to severe PMS, we assessed whether, among PMS cases, smoking was associated with the occurrence of specific menstrual symptoms. In studies of prevalent PMS, it may be difficult to determine whether smoking contributed to the onset of symptoms or whether menstrual symptoms themselves influence smoking behavior (29). To address this issue, we evaluated the impact of smoking both during adolescence and at the time of diagnosis. PMS cases who smoked at ages 15–19 years had a significantly higher risk of experiencing acne, anger, and backache and a significantly lower risk of cognitive symptoms such as headaches and insomnia. These symptoms were similarly associated with smoking status at the time of PMS diagnosis, at which point study participants had reached at least 29 years of age. The consistency of these associations over many years suggests that smoking may be etiologically related to the development of these specific symptom types.

Several other physical symptoms such as abdominal bloating and breast tenderness were related to smoking only at the time of diagnosis. It is possible that smoking may have a more immediate effect on the occurrence and/or the severity of physical symptoms. However, it is also plausible that women experiencing physical symptoms may be more likely to smoke as a means of self-medicating. Because only a few other studies have assessed the relation between smoking and specific menstrual symptoms (12, 19), additional research on smoking and the development of emotional, cognitive, and physical symptoms is needed to better understand these associations.

Despite public health efforts, cigarette smoking remains common among young women, including adolescent girls. Data from the 2005 Youth Risk Behavior Survey indicated that 26.0% of 12th-grade girls reported smoking cigarettes on 1 or more of the previous 30 days (30). Smoking on 20 or more days was reported by 12.5% of 12th-grade girls, and 9.2% reported smoking 10 or more cigarettes per day. Whereas smoking is associated with higher risk of heart disease, cancer, diabetes, and other conditions, it may be difficult for young women to decide not to smoke if they believe the adverse health consequences to be many years in the future. Because PMS and menstrual symptoms generally occur earlier in the life cycle than these other conditions, the knowledge that smoking may increase the likelihood of developing PMS may be more influential in convincing adolescent and young adult women to abstain.

Our study has several limitations. Because of the constraints of large prospective cohort studies, we were unable to use daily symptoms diaries to confirm incident diagnoses of PMS, as is the standard in clinical practice. However, in a recent study in our population, we found that prospective reporting of new PMS diagnoses combined with a short retrospective symptom questionnaire can accurately identify women with PMS (16). Although this method may not be as accurate as those used in clinical practice and intervention studies, it appears to be sensitive enough to identify risk factors for incident PMS (15, 16). In addition, because of the age of our participants at baseline (e.g., $\geq$27 years in 1991), we were not able to assess how smoking is associated with PMS developing at younger ages; consequently, our findings may be generalizable to only those women who develop PMS in their middle-to-older reproductive years. Although generalizability may also be limited by the fact that our participants are all registered nurses, such participants are probably more likely than most women to reliably report menstrual symptom experience and smoking level.

In summary, our results suggest that smoking, especially in adolescence and young adulthood, may substantially increase a woman's risk of developing moderate to severe PMS. Given the high prevalence of this behavior in young women, these findings may provide additional incentive for young women to avoid cigarette smoking.

ACKNOWLEDGMENTS

Author affiliations: Department of Public Health, School of Public Health and Health Sciences, University of Massachusetts, Amherst, Massachusetts (Elizabeth R. Bertone-Johnson); Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Susan E. Hankinson, JoAnn E. Manson); Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts (Susan E. Hankinson, JoAnn E. Manson); Department of Obstetrics and Gynecology, University of Iowa, Iowa City, Iowa (Susan R. Johnson); and Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (JoAnn E. Manson).

This work was supported by a grant from GlaxoSmithKline Consumer Healthcare; a cy pres distribution, Rexall/Cellasene settlement litigation (*Levine v Rexall Sundown, Inc*. (Los Angeles County Superior Court) No. BC 232370); and Public Health Services grant CA50385 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

The authors thank Dr. Walter C. Willett for his insightful comments on early versions of the manuscript.

Conflict of interest: none declared.

REFERENCES

1. Mortola JF, Girton L, Beck L, et al. Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument:

the calendar of premenstrual experiences. *Obstet Gynecol*. 1990;76(2):302–307.
2. Johnson SR. The epidemiology and social impact of premenstrual symptoms. *Clin Obstet Gynecol*. 1987;30(2): 367–376.
3. Sternfeld B, Swindle R, Chawla A, et al. Severity of premenstrual symptoms in a health maintenance organization population. *Obstet Gynecol*. 2002;99(6):1014–1024.
4. Deuster PA, Adera T, South-Paul J. Biological, social and behavioral factors associated with premenstrual syndrome. *Arch Fam Med*. 1999;8(2):122–128.
5. Johnson SR. Premenstrual syndrome therapy. *Clin Obstet Gynecol*. 1998;41(2):405–421.
6. Rapkin A. A review of treatment of premenstrual syndrome and premenstrual dysphoric disorder. *Psychoneuroendocrinology.* 2003;28(suppl 3):39–53.
7. Windham GC, Mitchell P, Anderson M, et al. Cigarette smoking and effects on hormone function in premenopausal women. *Environ Health Perspect*. 2005;113(10):1285–1290.
8. Verkasalo PK, Thomas HV, Appleby PN, et al. Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). *Cancer Causes Control*. 2001;12(1):47–59.
9. Sowers MF, Beebe JL, McConnell D, et al. Testosterone concentrations in women aged 25–50 years: associations with lifestyle, body composition, and ovarian status. *Am J Epidemiol*. 2001;153(3):256–264.
10. Redei E, Freeman EW. Daily plasma estradiol and progesterone levels over the menstrual cycle and their relation to premenstrual symptoms. *Psychoneuroendocrinology.* 1995; 20(3):259–267.
11. Halbreich U. The etiology, biology, and evolving pathology of premenstrual syndromes. *Psychoneuroendocrinology.* 2003; 28(suppl 3):55–99.
12. Kritz-Silverstein D, Wingard DL, Garland FC. The association of behavior and lifestyle factors with menstrual symptoms. *J Womens Health Gend Based Med*. 1999;8(9):1185–1193.
13. Strine TW, Chapman DP, Ahluwalia IB. Menstrual-related problems and psychological distress among women in the United States. *J Womens Health (Larchmt)*. 2005;14(4): 316–323.
14. Masho SW, Adera T, South-Paul J. Obesity as a risk factor for premenstrual syndrome. *J Psychosom Obstet Gynaecol*. 2005; 26(1):33–39.
15. Bertone-Johnson ER, Hankinson SE, Bendich A, et al. Calcium and vitamin D intake and risk of incident premenstrual syndrome. *Arch Intern Med*. 2005;165(11): 1246–1252.
16. Bertone-Johnson ER, Hankinson SE, Johnson SR, et al. A simple method for assessing premenstrual syndrome in large prospective studies. *J Reprod Med*. 2007;52(9):779–786.
17. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*. 1993;25(1):71–80.
18. Jun HJ, Rich-Edwards JW, Boynton-Jarrett R, et al. Intimate partner violence and cigarette smoking: association between smoking risk and psychological abuse with and without co-occurrence of physical and sexual abuse. *Am J Public Health*. 2008;98(3):527–535.
19. Willett WC. *Nutritional Epidemiology.* 2nd ed. New York, NY: Oxford University Press; 1998.
20. Gold EB, Bair Y, Block G, et al. Diet and lifestyle factors associated with premenstrual symptoms in a racially diverse community sample: Study of Women's Health Across the Nation (SWAN). *J Women's Health (Larchmt)*. 2007;16(5):641–656.
21. Mishra GD, Dobson AJ, Schofield MJ. Cigarette smoking, menstrual symptoms and miscarriage among young women. *Aust N Z J Public Health*. 2000;24(4):413–420.
22. Chuong CJ, Burgos DM. Medical history in women with premenstrual syndrome. *J Psychosom Obstet Gynaecol*. 1995; 16(1):21–27.
23. Friedman AJ, Ravnikar VA, Barbieri RL. Serum steroid hormone profiles in postmenopausal smokers and nonsmokers. *Fertil Steril*. 1987;47(3):398–401.
24. Khaw KT, Tazuke S, Barrett-Connor E. Cigarette smoking and levels of adrenal androgens in postmenopausal women. *N Engl J Med*. 1988;318(26):1705–1709.
25. Liu Y, Gold EB, Lasley BL, et al. Factors affecting menstrual cycle characteristics. *Am J Epidemiol*. 2004;160(2):131–140.
26. Rowland AS, Baird DD, Long S, et al. Influence of medical conditions and lifestyle factors on the menstrual cycle. *Epidemiology.* 2002;13(6):668–674.
27. Ilich JZ, Brownbill RA, Tamborini L, et al. To drink or not to drink: how are alcohol, caffeine and past smoking related to bone mineral density in elderly women? *J Am Coll Nutr.* 2002;21(6):536–544.
28. Thys-Jacobs S, Alvir MJ. Calcium-regulating hormones across the menstrual cycle: evidence of a secondary hyperparathyroidism in women with PMS. *J Clin Endocrinol Metab.* 1995;80(7):2227–2232.
29. Marks JL, Hair CS, Klock SC, et al. Effects of menstrual phase on intake of nicotine, caffeine, and alcohol and nonprescribed drugs in women with late luteal phase dysphoric disorder. *J Subst Abuse*. 1994;6(2):235–243.
30. Eaton DK, Kann L, Kinchen S. Youth risk behavior surveillance—United States, 2005. *MMWR Surveill Summ.* 2006;55(5):1–108.